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Original Paper

Medullary Carcinoma of the Breast. Prevalence and Prognostic Importance of Classical Risk Factors in Breast Cancer

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In an earlier study of 235 breast cancers with medullary features, we concluded from a multivariate Cox regression analysis that only four histopathological features contained significantly positive prognostic information. In the present study, continuing our work on the same population base, we used these histological characteristics (predominantly syncytial growth pattern, no tubular component, diffuse stromal infiltration with mononuclear cells and sparse necrosis (<25%), as diagnostic criteria for medullary carcinoma of the breast (MC). We found a significantly better prognosis for patients with MC than those with non-medullary carcinoma (NMC) or infiltrating ductal carcinoma (IDC). All tumours in the MC group were grade II or III (96% grade III). A significantly different distribution of general risk factors such as lymph node status, invasion, steroid receptor status, and menopausal status, was found between the group of MC and the control group of IDC grades II + III. Further, general risk factors, which are found to be of major prognostic importance in IDC, had little prognostic impact in MC. We found MC to be biologically unique, and patients with MC have a better than average prognosis compared to that of IDC. We propose a new histological definition of MC, but stress that prospective studies have to be performed.

Key words: breast cancer, medullary carcinoma of the breast, prognosis
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INTRODUCTION

IN A FORMER study on 235 cases of breast cancers with medullary features [1], we concluded from a multivariate Cox regression analysis that only four histopathological characteristics (predominantly syncytial growth pattern combined with no tubular component, diffuse stromal distribution of mononuclear cells and sparse necrosis) contained significant positive prognostic information. In addition, we demonstrated that these prognostically important histological features had a reasonable observer reproducibility [2]. We also found that diagnostic subgrouping in typical, atypical and non-medullary cancer as defined by Ridolfi and associates in 1977 [3] carried no significant prognostic importance, neither in the Cox analysis nor in the univariate analysis.

In the present study, we characterised medullary carcinoma of the breast (MC) in terms of prognosis, comparing it with a control group of infiltrating ductal carcinomas (IDC). We describe the distribution of other histopathological characteristics, and the prevalence and prognostic importance of generally well known risk factors for breast cancer and compare the results to IDC.

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MATERIALS AND METHODS

The histopathological material was the same as that described in a previously published paper [1]. Briefly, it consisted of 235 breast cancers registered as medullary carcinoma of the breast in protocols of the Danish Breast Cancer Cooperative Group (DBCG) from 1977 to 1987. A diagnostic subgroup was selected by stressing the diagnostic criteria of (1) predominantly syncytial growth pattern (> 75% of tumour area); (2) no tubular component; (3) diffuse stromal infiltration with mononuclear cells; and (4) sparse necrosis (< 25% of tumour area). Definition of syncytial growth pattern is based on Ridolfi's definition [3]: "Broad, interanastomosing sheets of tumour cells". The selected subgroup was labelled medullary carcinoma (MC) (Figure 1) and the remaining subgroup, i.e. the carcinomas not fulfilling the criteria, were called "non-medullary carcinoma" (NMC).

The following analyses were undertaken:

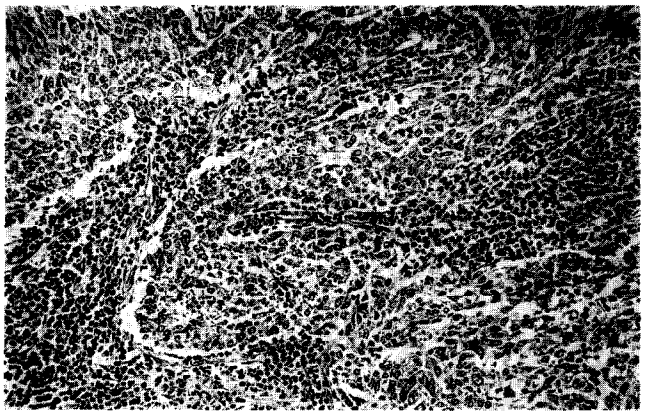

Figure 1. Typical appearance of medullary carcinoma. Notice the syncytial growth pattern and the diffuse mononuclear stromal infiltration (× 184).

1. A comparison of histological characteristics of the MC and NMC group: circumscription, grade of stromal mononuclear infiltration, nuclear pleomorphism and histological grade as defined by the WHO [4]. Observed distribution of histological features in the two diagnostic subgroups were compared using the χ^2 test. Histological evaluation of the tumour material was also described in two former studies [1, 3].

2. A comparison of the distribution of classical risk factors (lymph node status, tumour size, invasion, menopausal status, receptor status) in the MC and NMC groups, including IDC II + III as a control group. This control group was chosen, since none of the MC were graded I. Distribution of acknowledged risk factors for breast cancer in general, were described for the two subgroups (MC and NMC) and the control group of IDC, and distributions compared using the χ^2 test.

3. A comparison of the prognosis (recurrence-free and overall survival (RFS and OS)) of the MC, NMC subgroups with IDC grades II + III and IDC grade I serving as controls. For this analysis, IDC grade I was included because MC showed a better survival than the IDC grade II–III group. The prognoses of the four subgroups were illustrated with Kaplan–Meier plots and compared using log rank tests.

Clinical characteristics and survival data used in the present study were registered prospectively in the protocols of the DBCG for all three groups.

The organisation, design and follow-up of the nationwide DBCG programme and the protocols have been described in detail elsewhere [5]. Briefly, the primary surgical treatment was total mastectomy (in later years a minor group received tumorectomy only) and axillary sampling, and the patients were then allocated to a low risk and a high risk group according to risk factors. High risk was indicated by positive lymph node status and/or invasion of overlying skin or deep fascia and/or tumour > 5 cm. The low risk group had no adjuvant systemic treatment, while high risk group patients were allocated to adjuvant systemic treatment according to menopausal status. The content of steroid hormone receptors in the tumours was analysed in a single laboratory using the dextran-coated charcoal (DCC) method according to the EORTC recommendations [6]. When ≥ 10 fmol receptor/mg cytosol protein was found, the tumour was defined as being positive. Only 80 tumours (34%) were analysed for oestrogen receptor (ER) and 70 (29%) for progesterone receptor (PGR).

RESULTS

Table 1 presents the distribution of certain relevant histological features for the MC and NMC groups. Circumscription of two tumours (in the NMC group) could not be evaluated because the tumour margin was not sufficiently represented in the specimens. All tumours in the MC group were histological grades II and III with 96% grade III.

Table 2 describes the distribution of lymph node status, tumour size, invasion, risk groups, menopausal status and receptor status for the MC, NMC, and the control group. Risk group is a term used in the DBCG and serves the purpose of protocol allocation, which has been carefully described elsewhere [5]. Briefly, the high risk group consists of patients with lymph node metastases in the axilla and/or processus axillaris, and/or tumour > 5 cm, and/or invasion of deep resection line, and/or invasion of skin. The low risk group is defined as patients who do not have these factors. Not all clinical data were available for all the patients. Distribution of risk factors was almost the same in the MC and NMC groups, while several significant differences were found when comparing MC to IDC II + III, where the most outstanding difference concerned the content of steroid hormone receptors.

Table 3 presents data concerning age and tumour diameter. 53% of the tumours in the MC group were located in the left breast and 47% in the right. Most tumours were located in the upper lateral quadrant.

In Table 4, the prognostic importance of the aforementioned clinical parameters (risk factors) is shown for the diagnostic subgroups and the control group. All the risk factors were of highly significant prognostic importance in the control group of IDC grades II + III. In the MC group, only size was of significant prognostic importance for both RFS and OS, ER status was of significant prognostic importance for RFS, and menopausal

Table 1. Distribution of histological characteristics according to diagnostic subgroup (110 medullary carcinomas (MC) and 125 non-medullary carcinomas (NMC))

	MC *n* (%)	NMC *n* (%)	*P-value
Circumscription			
Complete circumscribed	77 (70)	68 (54)	
Monofocal infiltration	15 (14)	22 (18)	0.06
Multifocal infiltration	18 (16)	33 (26)	
Not evaluable	—	2 (2)	
Grade of stromal mononuclear infiltrate			
Sparse	17 (15)	62 (50)	
Moderate	71 (65)	52 (42)	0.0001
Marked	22 (20)	11 (9)	
Nuclear pleomorphism			
Slight	0	2 (2)	
Moderate	19 (17)	39 (31)	0.02
Marked	91 (83)	84 (67)	
Histological grade			
Grade I	0	2 (2)	
Grade II	4 (4)	23 (18)	0.001
Grade III	106 (96)	100 (80)	

*P-value calculated with χ^2 test for differences between MC and NMC groups.

Table 2. Distribution of known risk factors

	MC *n* (%)	NMC *n* (%)	IDC II+III *n* (%)	*P*-values MC versus NMC	*P*-values MC versus IDC II+III
Lymph node status					
Negative	70 (64)	77 (63)	3199 (51)		
Positive	40 (36)	46 (37)	3037 (49)	≥ 0.15	0.01
1–3 nodes	28 (25)	30 (24)	1925 (31)		
≥ 4 nodes	12 (11)	16 (13)	1112 (18)	≥ 0.15	≥0.15
Size					
<2 cm	50 (51)	53 (45)	2436 (45)		
2–5 cm	41 (42)	50 (42)	2481 (46)	≥ 0.15	≥0.15
>5 cm	7 (7)	15 (13)	482 (9)		
Invasion*					
Negative	100 (93)	107 (86)	5211 (84)	0.09	0.01
Positive	8 (7)	18 (14)	1018 (16)		
Risk group †					
Low	60 (55)	69 (55)	2802 (45)	≥ 0.15	0.04
High	50 (45)	56 (45)	3482 (55)		
Menopausal status					
Pre	66 (60)	58 (46)	2727 (43)	0.04	0.001
Post	44 (40)	67 (54)	3549 (57)		
Receptor status					
ER-positive	12 (33)	13 (30)	1265 (71)		
ER-negative	24 (67)	31 (70)	527 (29)	≥ 0.15	<0.0001
PGR-positive	12 (36)	9 (24)	983 (64)		
PGR-negative	21 (64)	28 (76)	554 (36)	≥ 0.15	0.001

Not all data were available for all the patients (particularly receptor status). *Invasion considered positive when there was spread of the tumour to overlying skin or deep fascia; †High risk group consists of patients with lymph node metastases in axilla and/or processus axillaris, and/or tumour > 5 cm, and/or invasion of deep resection line, and/or invasion of skin. Low risk patients are defined as those not having these factors.
MC, medullary carcinoma of the breast; NMC, non-medullary carcinoma; IDC, infiltrating ductal carcinomas; ER, oestrogen receptor; PGR, progesterone receptor.

Table 3. Age and tumour size

	MC (n = 110)	NMC (n = 125)	IDC II+III (n = 6284)
Age (years)			
Mean	50	53	56
Median	48	52	56
Greatest diameter of tumour			
Mean (cm)	2.8	3.2	3.0
Median (cm)	2.0	2.5	2.5

For abbreviations see legend to Table 2.

status for OS, with premenopausal patients having the better survival. Lymph node status was also of significant prognostic information for OS, but only stratified as negative, one to three lymph nodes and four or more lymph nodes. The 5 and 10 year survival figures for RFS and OS, including 95% confidence limits, are given in Tables 5 and 6.

Figures 2 and 3 present the RFS and overall survival curves for MC, NMC, and the two control groups of IDC grades II + III and IDC grade I. For both RFS and OS, MC had a significantly better prognosis than NMC (P_{RFS} = 0.0005; P_{OS} = 0.001) and IDC grade II + III (P_{RFS} = 0.001; P_{OS} = 0.002). Survival was largely the same for the MC and IDC grade I groups, and for the NMC and IDC grades II + III groups. Patients with MC also had a significantly better survival than those with IDC grade I–III (P_{RFS} = 0.03; P_{OS} = 0.006) (data not shown).

Table 4. Prognostic importance of known risk factors

	MC (n = 110)		NMC (n = 125)		IDC II+III (n = 6284)	
	RFS	OS	RFS	OS	RFS	OS
Lymph node status						
Negative versus positive	N.S.	N.S.	0.11	0.0003	<0.0001	<0.0001
Negative versus 1–3 versus ≥4	N.S.	0.01	0.01	<0.0001	<0.0001	<0.0001
Size						
0–2 cm versus > 2 cm	0.04	0.004	N.S.	N.S.	<0.0001	<0.0001
Invasion*						
Negative versus positive	N.S.	N.S.	0.02	0.01	<0.0001	<0.0001
Risk group						
Low versus high	N.S.	0.12	0.11	0.0002	<0.0001	<0.0001
Menopausal status						
Pre versus post	N.S.	0.01	N.S.	N.S.	<0.0001	<0.0001
Receptor status						
ER-positive versus ER-negative	0.05	0.12	N.S.	N.S.	<0.0001	<0.0001
PGR-positive versus PGR-negative	0.09	N.S.	N.S.	0.13	<0.0001	<0.0001

Kaplan–Meier plots were drawn for individual risk factors in each histological subgroup and compared by log rank test.
*Invasion registered as positive when spread of the tumour to overlying skin or deep fascia.
N.S.: $P \geq 0.15$. Trend: $0.14 > P \geq 0.05$. Significant: $P < 0.05$.
RFS, recurrence-free survival; OS, overall survival. For other abbreviations see legend to Table 2.

Figure 4 illustrates that for MC, the prognostic survival for patients with between one and three positive axillary lymph nodes was the same as for patients with no positive lymph nodes, and significantly better ($P = 0.004$) than for patients with four or more positive lymph nodes. The group of NMC and those with IDC II + III lymph node negative had a better survival than patients with between one and three lymph nodes, although the latter had a better survival than patients with four or more positive nodes. The differences were highly significant both when stratifying for number of nodes and when only stratifying for negative and positive nodes (Table 4).

DISCUSSION

We selected a group of 110 patients with MC who we found had a highly significant better survival compared with those with either NMC or IDC grades II + III. The group of MC also had a significantly better survival than patients with IDC grade I–III. These observations justify our recently developed histological criteria for MC [1]. The prognosis of patients with MC corresponded to that of those with IDC histological grade I. With this in mind, it is interesting to see that none of the MCs were histological grade I and that most were grade III (96%). These observations concur with those by Schiødt [7] and Gorski and associates [8], who both found that medullary carcinomas histological grade III had a significantly better prognosis than other types of histological grade III breast cancers. It is also interesting that significantly fewer NMCs were histological grade III (80%). The same observation could be made for nuclear pleomorphism, with 83% of MCs and 67% of NMCs displaying marked nuclear pleomorphism. MC was also characterised by having mainly moderate (or marked) stromal mononuclear infiltration, while in NMCs this was mainly sparse or moderate, the difference being highly significant. Concerning circumscription, most MCs were completely circumscribed, but 30% still exhibited monofocal or multifocal infiltration. Circumscription, moderate to marked grade of mononuclear infiltrate and high histological and nuclear grade are all part of the diagnostic set of criteria for typical medullary carcinoma (TMC) as defined by Ridolfi and associates in 1977 [3]. Criteria, which we share with Ridolfi, are syncytial growth and absence of tubular component. These features were found to be of major prognostic importance in our earlier study [1], where none of Ridolfi's other histological characteristics were found to carry significant prognostic impact. We found, however, that most tumours in our MC group were characterised by these histological features, especially high histological and nuclear grade and, to a lesser extent, circumscription. This distribution of histological features in the MC group might, of course, be caused by our population base. Concerning the definition of typical and atypical medullary carcinoma (TMC and AMC) by Ridolfi and associates [3], which is probably the most widely used definition among pathologists today, we found it to be of no prognostic value in our hands [1], neither in the univariate nor in the multivariate regression analysis. In another study, we found the inter- and intra-observer variability when using this definition to be considerable and to have significant prognostic implications [9]. The studies of Rapin and associates [10] and Wargotz and Silverberg [11] have, however, shown excellent survival for TMC when using the criteria of Ridolfi and associates [3]. Still, the numbers in both studies were very small (26 TMC and 24 TMC, respectively).

When characterising our group of MC for general risk factors for breast cancers, it is noteworthy that a significantly higher proportion of patients were lymph node negative (axillary) in the MC group than in the control group of IDC grades II + III. Fisher and associates, in their recent article on MC [12], also found a significantly lower frequency of metastatic deposits in axillary lymph nodes in patients with TMC than with IDC_{NOS}. Others have also found a relatively low frequency of lymph node metastases with MC [7, 10, 11, 13–15]. In our study, this observation cannot explain the better prognosis of MC, as lymph node status stratified as negative and positive nodes has no significantly prognostic importance for those with MC. In the control group of IDC grades II + III and those with NMC, the corresponding prognostic importance was highly significant.

Table 5. Five and 10 year recurrence-free survival rates (RFS)

	MC (n = 110)				NMC (n = 125)				IDC II+III (n = 6284)			
	RFS 5 years		RFS 10 years		RFS 5 years		RFS 10 years		RFS 5 years		RFS 10 years	
	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
Lymph node status												
Negative	67	(55–78)	65	(54–76)	54	(42–65)	45	(33–58)	61	(59–63)	47	(45–49)
Positive	73	(59–88)	70	(55–85)	39	(25–53)	28	(15–42)	42	(40–44)	30	(28–31)
1–3 positive	77	(61–93)	77	(61–93)	50	(32–68)	41	(22–60)	51	(49–53)	38	(36–40)
> 4 positive	66	(39–93)	56	(26–85)	19	(0–38)	–	–	26	(23–28)	15	(12–17)
Size												
0–2 cm	79	(67–90)	79	(67–90)	49	(35–62)	40	(26–55)	62	(60–64)	48	(46–50)
> 2 cm	62	(48–76)	59	(45–73)	47	(34–59)	36	(23–49)	43	(41–45)	31	(29–33)
Invasion												
Negative	71	(62–80)	68	(59–78)	51	(41–61)	42	(32–52)	55	(53–56	41	(40–43)
Positive	50	(15–85)	–	–	25	(4–45)	16	(0–35)	37	(34–40)	25	(22–28)
Risk group												
Low	70	(58–81)	67	(55–80)	55	(43–66)	45	(32–58)	61	(60–63)	48	(46–50)
High	68	(55–82)	66	(52–79)	38	(26–51)	29	(17–42)	44	(42–46)	31	(29–33)
Menopausal status												
Pre	68	(57–79)	68	(57–79)	44	(32–57)	35	(21–48)	53	(51–55)	43	(41–45)
Post	71	(57–85)	65	(50–80)	50	(38–62)	41	(28–54)	51	(49–52)	35	(33–37)
Receptor status												
ER-positive	91	(74–100)	–	–	58	(30–87)	26	(0–59)	53	(50–56)	38	(35–42)
ER-negative	58	(38–78)	58	(38–78)	42	(25–59)	39	(21–56)	45	(41–49)	36	(32–41)
PGR-positive	91	(75–100)	–	–	56	(23–88)	–	–	53	(50–56)	38	(35–42)
PGR-negative	62	(41–83)	62	(41–83)	43	(24–61)	34	(13–55)	44	(40–48)	35	(30–39)

For abbreviations see legend to Table 2.

When further substratifying nodal staus into negative, between one and three nodes, and four or more nodes, there was a significant prognostic importance for OS in the MC group, but patients with one–three positive lymph nodes have a similar survival to that of lymph node negative patients. This is in contrast to the two other histological subgroups, and might partially explain the more favourable outcome of MC. For MC, we can thus select a small group of patients (11%) with four or more positive nodes, who follow an aggressive course. However, the patient numbers in the substratified groups was rather small, and the result needs to be confirmed in other studies before any therapeutic consequence should be defined.

No significant differences were observed between the histological groups for tumour size, and this parameter was the only one with significant importance for both RFS and OS. A significantly lower frequency of invasion of the skin or deep fascia was found for MC compared with IDC grades II + III and NMC. The prognostic importance of invasion for survival was highly significant for patients with IDC grades II + III, significant for NMC patients, but had no significant prognostic impact for patients with MC.

Risk groups were defined by the three general risk factors mentioned above, the high risk group being indicated by positive lymph node status, and/or tumour size > 5 cm, and/or positive invasion. In the DBCG, high risk patients are randomised to different adjuvant treatments according to menopausal status [5]. Parallel to observations on lymph node status and invasion, a significantly smaller number of patients were found to be high risk patients in the MC group than in the other groups, and no significant impact of risk group on survival was observed for MC patients. The opposite was found in the other groups. However, a trend was observed in the MC group indicating a better survival for low risk patients.

There were significantly more premenopausal patients in the MC group than in the control group of IDC grades II + III, and premenopausal patients had a significantly better OS in both groups. Maier and colleagues [14] also found a significantly better survival for premenopausal patients with MC than for postmenopausal patients. Correpondingly, there was also a tendency of lower mean and median age in patients with MC than in patients with IDC grades II + III. This observation concurs with that of others [16].

Analyses were performed for only a minor proportion of the patients for steroid receptor status. To the best of our knowledge this is, however, the most comprehensive study on steroid receptor status and its prognostic importance in MC. For the MC group, we found an ER receptor-positive frequency of 33%, which was significantly smaller than that of the control group of

Table 6. Five and 10 year overall survival rates (OS)

	MC				NMC				IDC II+III			
	OS 5 years		OS 10 years		OS 5 years		OS 10 years		OS 5 years		OS 10 years	
	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
Lymph node status												
Negative	84	(76–93)	79	(70–89)	73	(63–83)	62	(50–74)	79	(78–81)	59	(58–61)
Positive	78	(65–90)	72	(58–86)	46	(31–60)	33	(18–47)	54	(53–56)	37	(35–39)
1–3 positive	86	(73–99)	82	(68–96)	57	(39–74)	48	(29–67)	64	(62–67)	46	(43–48)
⩾ 4 positive	58	(30–86)	49	(21–78)	25	(4–46)	–	–	37	(34–40)	21	(18–23)
Size												
0–2 cm	90	(82–98)	88	(79–97)	64	(51–77)	54	(40–68)	78	(76–79)	59	(57–61)
> 2 cm	73	(60–85)	64	(50–78)	60	(48–72)	49	(36–61)	58	(56–60)	40	(38–42)
Invasion												
Negative	82	(74–90)	79	(71–87)	64	(55–74)	55	(45–65)	71	(69–72)	51	(50–53)
Positive	88	(65–100)	56	(17–95)	44	(21–67)	26	(5–47)	50	(46–53)	33	(30–36)
Risk group												
Low	83	(74–93)	83	(74–93)	74	(64–84)	64	(51–76)	80	(79–82)	60	(58–62)
High	80	(69–91)	69	(55–82)	46	(33–59)	33	(20–46)	56	(55–58)	39	(37–41)
Menopausal status												
Pre-	88	(80–96)	83	(73—92)	60	(48–73)	49	(35–63)	70	(68–72)	55	(53–57)
Post-	73	(60–86)	68	(54–82)	63	(51–74)	51	(38–64)	65	(63–66)	43	(41–45)
Receptor status												
ER-positive	92	(76–100)	–	–	77	(54–100)	38	(6–71)	70	(68–73)	50	(47–53)
ER-negative	71	(53–89)	60	(38–81)	55	(37–72)	55	(37–72)	54	(50–59)	42	(37–47)
PGR-positive	83	(62–100)	–	–	78	(51–100)	–	–	71	(68–74)	51	(47–54)
PGR-negative	76	(58–94)	65	(43–86)	53	(35–72)	42	(22–62)	55	(51–59)	39	(34–44)

For abbreviations see legend to Table 2.

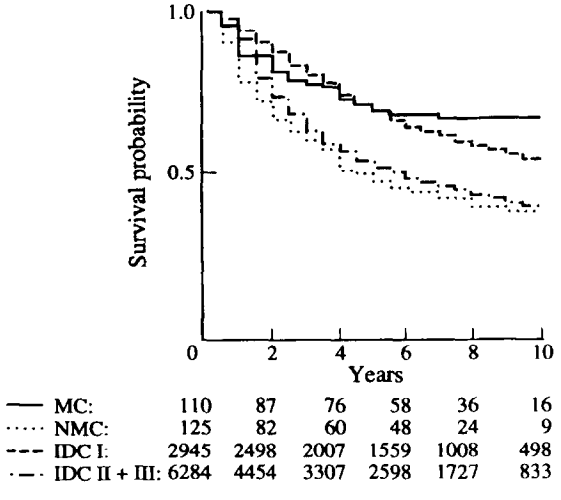

Figure 2. Kaplan–Meier plots of recurrence-free survival (RSF) for medullary carcinoma of the breast (MC), the complementary group of non-medullary carcinoma (NMC), and the control groups of infiltrating ductal carcinomas histological grade I (IDC I) and grade II + III (IDC II + III). Patients at risk are given under the abcissa.

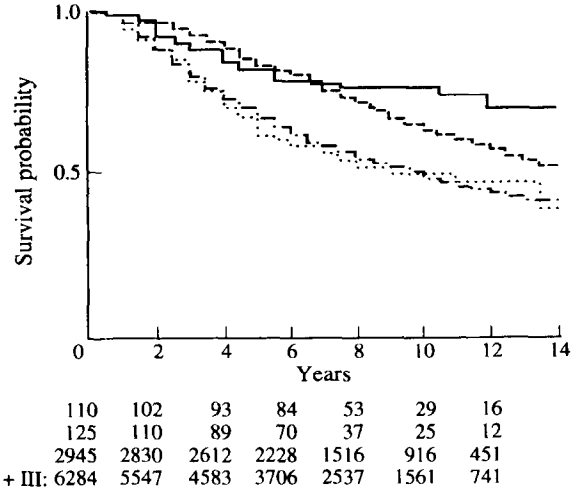

Figure 3. Kaplan–Meier plots of overall survival for MC, NMC, IDC I and IDC II + III. Patients at risk are given under the abcissa.

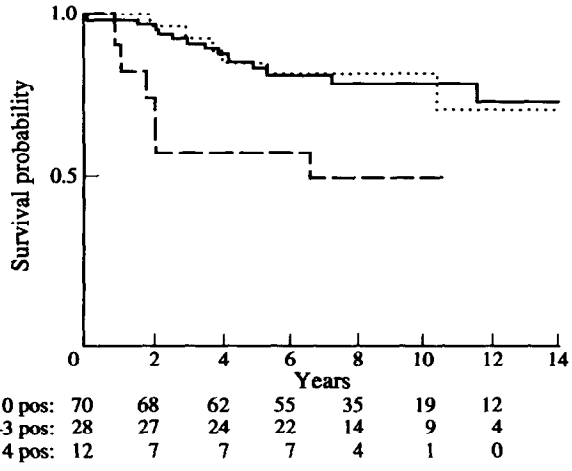

Figure 4. Kaplan–Meier plots of overall survival for MC, stratified into lymph node negative, 1-3 positive lymph nodes and ≥4 positive lymph nodes. Patients at risk are given under the abcissa.

IDC II + III (71%), but equal to the frequency of ER positivity in the NMCs. This low frequency of ER positivity in MC is well known from other studies [12, 13, 16–19]. In his recent article on MC [12], Fisher and associates reported an ER positivity of 11% in 138 patients with node-negative MC. Mitze and Goepel [13] in 37 MCs found 30% to be ER-positive, and Ponsky and associates [17] described a 25% ER positivity in 20 MCs. For PGR we also found a low incidence of positivity in both the MC group and the NMCs (significantly lower than for the control group of IDC grades II +III). This is also in line with other studies [13, 17]. It is a paradox that this tumour, having the better prognosis, has such a low frequency of steroid receptor positivity. We found a significantly better RFS for ER-positive than for ER-negative patients, but PGR status had no impact on survival. However, from the actual survival figures, it is evident that the ER receptor-positive patients had a better survival than the receptor-negative patients. The numerical difference is even greater for MC than it is for IDC, but because of the small number of patients with receptor status, the difference was not significant. This is in contrast to the control group, where both receptors have a highly significant impact on prognosis.

The prognostic importance of the general risk factors in the group of NMC seems to be somewhere between that for the MC and IDC II + III groups. Survival curves for patients with MC were different from those with IDC. For IDC, a gradual decline in RFS and OS was seen during the 12 years of observation, while the RFS and OS for MC were almost stable after 6 years. Others have made similar observations [3, 12].

In conclusion, we re-affirm the previously proposed definition of MC [1], which is based on the following histological features: (1) predominantly syncytial growth pattern and no tubular component; (2) diffuse stromal infiltration with mononuclear cells; and (3) sparse (< 25%) necrosis. We found a highly sigificant, better survival for patients with MC than those with NMC or IDC. MC is biologically different from other breast cancers, with patients having a significantly different distribution of general risk factors, such as lymph node status, invasion, receptor status and menopausal status. Further, these risk factors, which are found to be of major prognostic importance in breast cancer in general, have minimal prognostic value in MC. Of course the prognostic importance of this new definition of MC has to be validated in a prospective study, which we are addressing.

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